



Mishra, E. K., Clive, A. O., Wills, G. H., Davies, H. E., Stanton, A. E., Al-Aloul, M., Hart-Thomas, A., Pepperell, J., Evison, M., Saba, T., Harrison, R. N., Guhan, A., Callister, M. E., Sathyamurthy, R., Rehal, S., Corcoran, J. P., Hallifax, R., Psallidas, I., Russell, N., ... Rahman, N. M. (2018). Randomized Controlled Trial of Urokinase versus Placebo for Nondraining Malignant Pleural Effusion. *American Journal of Respiratory and Critical Care Medicine*, 197(4), 502-508.
<https://doi.org/10.1164/rccm.201704-0809OC>

Peer reviewed version

Link to published version (if available):
[10.1164/rccm.201704-0809OC](https://doi.org/10.1164/rccm.201704-0809OC)

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PDF-document

This is the author accepted manuscript (AAM). The final published version (version of record) is available online via ATS at <https://www.atsjournals.org/doi/full/10.1164/rccm.201704-0809OC>. Please refer to any applicable terms of use of the publisher.

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Randomised Controlled Trial of Urokinase versus Placebo for Non-draining Malignant Pleural Effusion

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58 Figures: GHW

59

60 Sources of support: Funding was provided by the National Cancer Research

61 Institute. Urokinase and placebo were provided by Syner-Med Ltd.

62

63 Running head: Intrapleural urokinase for malignant effusions

64

65 Descriptor number: 9.31

66

67 Total word count: 2,974

68

69 This article has an online data supplement which is accessible from this issue's table

70 on content online at www.atsjournals.org.

71

72 **At a Glance Commentary**

73 **Scientific Knowledge on the Subject:** Two previous trials of intrapleural fibrinolytics
74 for malignant pleural effusion demonstrated a significant increase in pleural fluid
75 drainage, lung re-expansion, a decrease in requirement for supplementary oxygen
76 therapy but no difference in recurrence rate following pleurodesis in the first 30 days.

77 **What this study adds to the field:** In this randomized controlled trial of intrapleural
78 urokinase versus placebo in 71 patients with non-draining malignant pleural effusion
79 despite the presence of a patent chest tube, there was no difference in the key
80 clinical outcomes of dyspnea or time to pleurodesis failure over 1 year. Alternative
81 palliative measures should be used to relieve breathlessness in this patient group.

82 **Abstract**

83 **Rationale:** Patients with malignant pleural effusion (MPE) experience breathlessness,
84 which is treated by drainage and pleurodesis. Incomplete drainage results in residual
85 dyspnea and pleurodesis failure. Intrapleural fibrinolytics lyse septations within
86 pleural fluid, improving drainage.

87 **Objectives:** To assess the effects of intrapleural urokinase on dyspnea and
88 pleurodesis success in patients with non-draining malignant effusion.

89 **Methods:** Prospective double blind randomised trial; patients with non-draining
90 effusion were randomly allocated 1:1 to intrapleural urokinase (100,000 IU three
91 doses 12 hourly) or matched placebo.

92 **Measurements:** Co-primary outcome measures: dyspnea (average daily 100mm
93 visual analogue scores over 28 days) and time to pleurodesis failure to 12 months.
94 Secondary outcomes: survival, time in hospital and radiographic change.

95 **Main results:** 71 subjects randomised (36 received urokinase, 35 placebo) from 12 UK
96 Centres. Baseline characteristics were similar between groups. There was no
97 difference in mean dyspnea between groups (mean difference 3·8mm, 95% CI -12 to
98 4·4mm, $p=0\cdot36$). Pleurodesis failure rates were similar (urokinase 13/35 (37%),
99 placebo 11/34 (32%), adjusted hazard ratio 1·2, $p=0\cdot65$). Urokinase was associated
100 with a decreased effusion size on chest radiograph (adjusted relative improvement -

101 19% (95% CI -28 to -11%, $p < 0.001$), reduced hospital stay (1.6 days (95% CI 1.0 to
102 2.6), $p = 0.049$) and improved survival (69 days versus 48 days, $p = 0.026$).

103 **Conclusions:** Use of intrapleural urokinase does not reduce dyspnea or improve
104 pleurodesis success compared with placebo, and cannot be recommended as an
105 adjunct to pleurodesis. Other palliative treatments should be used. Improvements in
106 hospital stay, radiographic appearance and survival associated with urokinase require
107 further evaluation.

108 **Abstract word count:** 250

109 **Key words:** fibrinolytic, pleurodesis, dyspnea

110

111 **Trial registration information:**

- 112 • ISRCTN (www.isrctn.com): 12852177
- 113 • EudraCT (<https://eudract.ema.europa.eu>): 2008-000586-26
- 114 • MREC (nih.gov.my/web/mrec/): 09/H0604/5

115

116 **Introduction**

117 Malignant pleural effusion (MPE) is common, affecting an estimated 200,000 patients
118 in the UK and USA per year(1, 2), and causes disabling dyspnea(3). Standard
119 treatment involves drainage via chest tube, followed by artificial synthesis of the
120 pleural membranes (pleurodesis) to prevent recurrence(3). However, initial drainage
121 may be incomplete resulting in persistent breathlessness and preventing effective
122 pleurodesis. This is due to fibrinous adhesions within the pleural space, dividing the
123 fluid into septations(4). Ultrasound images demonstrate intrapleural fibrinolytics lyse
124 adhesions and improve drainage in MPE(5).

125 While fibrinolytics alone are of no value in pleural infection(6, 7), two small trials of
126 intrapleural fibrinolytics for MPE suggest some benefit(8, 9). Okur et al. randomised
127 47 patients to either streptokinase or no treatment and demonstrated a significant
128 increase in pleural fluid drainage and lung re-expansion, but no difference in
129 recurrence rate following pleurodesis(9). Saydam, et al. conducted a randomised trial
130 of streptokinase or saline in 40 patients with loculated MPE visible on computer
131 tomography(8), demonstrating significantly increased drainage, a decrease in
132 requirement for supplementary oxygen therapy, and a non-significant decrease in
133 pleural fluid recurrence in the first month following streptokinase. However, no trial to
134 date has assessed the utility of intrapleural fibrinolysis on clinically meaningful
135 outcomes in this population.

136 This trial was conducted to assess the effect of adjunctive intrapleural urokinase on
137 improving pleurodesis, addressing the key clinical outcomes of dyspnea and

pleurodesis success in patients with non-draining MPE. Some of the results of this study have previously been reported in the form of an abstract(10).

Methods

Study design

The third Therapeutic Intervention in Malignant Effusion Trial (TIME3) was a double-blind, placebo-controlled randomised trial recruiting in 12 British hospitals. Ethical and regulatory approval for the study was obtained from NRES South Central – Oxford A, UK before recruitment commenced and the trial was registered (ISRCTN: 12852177, EudraCT number: 2008-000586-26, MREC number: 09/H0604/5). The trial was overseen by a Trial Steering Committee that met annually, and by a Data Monitoring Committee.

Participants

Adult participants with a diagnosis of MPE with a patent, correctly sited chest tube inserted for dyspnea relief, and significant residual pleural fluid gave written informed consent prior to enrolment. The diagnosis was established by either histo-cytological proof of pleural malignancy, or a recurrent large pleural effusion in the context of histologically-proven cancer outside the pleural space. For inclusion, patients initially required >25% opacification of the hemithorax by residual fluid on chest radiograph, but this was altered in March 2011 to either: >15% opacification of the hemithorax on chest radiograph; or, >2cm loculated pleural fluid visible on ultrasound. This trial

160 modification was made in response to increasing use of thoracic ultrasound in clinical
161 practise in UK and to improve study recruitment.

162 Exclusion criteria were: age <18 years, expected survival <28 days, known
163 underlying trapped lung of sufficient severity that pleurodesis is futile, previous
164 lobectomy or pneumonectomy on the side of the effusion, pleural infection, previous
165 intrapleural fibrinolytics, known urokinase allergy, coincidental stroke, major
166 haemorrhage or major trauma, major surgery in the previous 5 days, chylothorax,
167 pregnancy, lactating mothers, irreversible bleeding diathesis or platelet count
168 $<100 \times 10^9$, irreversible visual impairment and inability to consent or comply with the
169 protocol. Initially, patients with highly chemotherapy-responsive tumours, such as
170 small-cell lung cancer were excluded unless the patient had already undergone
171 chemotherapy, but this exclusion criterion was removed in March 2011.

172

173 **Randomisation and masking**

174 Patients were randomised in a 1:1 ratio to urokinase or matched identical placebo
175 using minimisation, with a random component of 80%, using a telephone
176 randomization service provided by the Medical Research Council Clinical Trials Unit,
177 London. Code break was only available to the trial statistician and this was not
178 required at any time during the trial. Minimisation criteria were histologic tissue type
179 (mesothelioma versus non-mesothelioma), previous pleurodesis (yes or no), World
180 Health Organisation (WHO) performance status (0-2 or 3/4) and recruiting centre(11).

181 Treating physicians, patients and outcome assessors were blinded to treatment
182 allocation throughout the study.

183

184 **Baseline assessments (day 0)**

185 At baseline, patients completed a 100mm visual analogue scale (VAS) score
186 assessing dyspnea over the preceding 24 hours. The VAS has previously been
187 validated to assess dyspnea in pleural disease(12) and consists of a 100mm line
188 anchored with “no breathlessness” at 0mm and “maximum possible breathlessness”
189 at 100mm(13). Patients were asked to mark the line at a point representing their level
190 of dyspnea. Patients completed the European Organisation for Research and
191 Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-30)(14) and
192 baseline demographic and treatment data were recorded.

193

194 **Trial interventions**

195 Three doses of urokinase (100,000 units) or exactly matched placebo vials were
196 reconstituted in 20ml 0.9% saline and injected intrapleurally at 12 hourly intervals via
197 the chest tube (days zero to one). Twenty-four hours following the last dose (day
198 two), a chest radiograph was obtained and talc slurry pleurodesis performed with 4g
199 sterile high grade talc (Novatech, France) following trial specific procedures based on
200 the national British Thoracic Society treatment guidelines(3). Pleurodesis was
201 performed regardless of ongoing fluid drainage volume and chest radiograph

202 appearance. The chest tube was removed once significant drainage (>150mls in
203 each 24 hour period) had ceased.

204 All participants received treatment of the causative primary tumour in accordance
205 with current guidelines and oncological advice.

206

207 **Trial assessments**

208 Patients were followed up for 12 months after randomization or until death. Patients
209 completed VAS scores at the same time each day for 28 days and at the three, six
210 and twelve month assessment points.

211 Data on pleurodesis failure, the EORTC QLQ-30 questionnaire, assessment of
212 complications, and health care utilisation were measured at 28 days and three, six
213 and 12 months. All adverse events (AEs) occurring within the first three days
214 following randomisation were recorded.

215

216 **Trial outcomes**

217 *Primary Outcomes*

218 The two co-primary outcome measures were:

- 219 1. Mean daily dyspnea over the first 28 days post-enrolment measured by VAS. All
220 patient completed VAS scores were measured by two independent researchers
221 and the mean measurement used.

222 2. Time to pleurodesis failure, defined as symptomatic ipsilateral pleural fluid
223 recurrence. This required one of the following, to ensure clinical applicability of
224 the study result:

- 225 • A further ipsilateral drainage procedure to control breathlessness; or
- 226 • Symptomatic pleural fluid recurrence as determined by the physician caring for
227 the patient where a further procedure was not conducted (for reasons
228 including patient choice, futility or other medical reason (e.g. anticoagulation,
229 poor performance status)).

230

231 *Secondary Outcomes*

232 Predetermined secondary outcomes were:

- 233 1. Radiographic change in the area of the pleural effusion (measured as the
234 difference in the proportion of the ipsilateral hemithorax occupied by the
235 pleural effusion opacity on chest radiograph) on day two post randomisation.
236 The chest radiograph pleural opacity was measured using a validated digital
237 system as has been reported previously(6).
- 238 2. Total volume of pleural fluid drained post-randomisation.
- 239 3. All cause mortality to 12 months.
- 240 4. Length of hospital stay post randomisation.
- 241 5. Frequency of serious and non-serious adverse events.
- 242 6. Blood parameters including biochemical and full blood count analysis.

243

244 **Statistical Methods**

245 Data were analysed on an intention-to-treat basis, and all randomised patients in
246 whom an outcome was available were included in the analysis. Analyses were pre-
247 determined prior to data analysis and a full Statistical Analysis Plan was signed off
248 prior to assessment of any data (full details available in the online supplement).

249 Analyses were adjusted for minimisation criteria (performance status, mesothelioma
250 and previous pleurodesis)(15). Stata version 12.1 was used (StataCorp. 2011).

251 The difference between treatment groups in mean daily dyspnea VAS score over 28
252 days was calculated using a mixed-effects linear regression model, to account for
253 days with missing VAS scores (as an unbiased analysis which does not differentiate
254 between scores missing due to patient death and those missing because the patient
255 did not complete their VAS score on that day). Study day was modelled as a
256 continuous variable using fractional polynomials and was included in the model as a
257 random effect. The model adjusted for the baseline VAS score(16) to increase
258 statistical precision.

259 Time to pleurodesis failure was analysed using a competing risk model, with death as
260 the competing risk.

261 Mean change in area of pleural effusion on day two (after receipt of trial drug, but
262 prior to pleurodesis) was calculated using a linear regression model, adjusting for
263 baseline proportion.

264 **Sample Size Calculation**

265 For the pleurodesis outcome, a 32% pleurodesis failure rate in the urokinase group
266 and an 80% failure rate in the placebo group was assumed. With 25% loss to follow

267 up (from expected mortality known in MPE), 68 patients were required, with 90%
268 power, 5% significance level.

269 For the dyspnea outcome, power calculations based on pilot data from patients with
270 MPE indicated 126 patients were needed to detect a 7mm difference in VAS for
271 breathlessness (SD =11mm, 90% power, alpha =0.05, with 25% loss to FU), and
272 therefore a recruitment target of 126 patients was chosen. Towards the end of
273 recruitment, data published demonstrated the minimally important difference of the
274 VAS score for dyspnea for patients with pleural effusion was 19mm (95% CI 14-
275 24mm) (12), and using this new data, the sample size required to detect a clinically
276 important difference in dyspnea would have been 40 patients.

277

278

279 **Results**

280 The trial CONSORT flow chart is presented in Figure 1. Seventy one patients were
281 recruited from 12 UK hospitals between 1st September 2009 and 30st June 2014, with
282 recruitment ending due to expiry of the placebo medication. 36 patients were
283 randomised to urokinase and 35 to placebo, with the treatment groups well matched
284 at baseline (table 1).

285

286 **Change in VAS dyspnea scores**

287 In both groups, baseline VAS score was 38mm (standard deviation (SD) 28mm in
288 urokinase, 25mm in placebo) (table 1). Mean VAS dyspnea over 28 days was 39mm
289 in the urokinase group and 35mm in the placebo group, equating to an average
290 mean difference in VAS score over 28 days from baseline of 1.4mm (SD 20mm) in
291 the urokinase and -3.2mm (SD 21mm) in the placebo groups respectively. There was
292 no significant difference between the two groups (adjusted mean difference from
293 baseline between groups -3.8mm, 95% CI -12 to 4.4mm, $p=0.36$) (Figure 2).
294 Outcome data was missing in eight patients (three in urokinase group, five in
295 placebo) due to the following reasons: baseline VAS score only (1); VAS booklets not
296 returned (7). A total of 34 patients died during the first 28 days post randomisation
297 (19 urokinase, 15 placebo).

298 There was no difference in the number of patients achieving a clinically significant
299 decrease in VAS dyspnea (≥ 19 mm) between the two groups (urokinase 13 patients,
300 placebo 15 patients, $p=0.09$).

301

302 **Pleurodesis success**

303 There was no significant difference in time to pleurodesis failure, which occurred in
304 13/35 (37%) of patients receiving urokinase compared with 11/34 (32%) receiving
305 placebo (adjusted hazard ratio 1.2, $p=0.65$) (Figure 3). Two patients were excluded
306 from analysis due to death occurring within three days of randomisation (one in each
307 treatment group).

308

309 **All cause mortality up to 12 months**

310 Death occurred by 12 months of follow up in 31/36 patients in the urokinase group
311 and in all patients in the placebo group. Median time to death after randomisation
312 was significantly more in the urokinase group, with median survival of 69 (IQR 24-
313 123) days in the urokinase group and 48 (IQR 31-80) days in the placebo group
314 (adjusted analysis for minimisation factors, $p=0.026$).

315

316 **Radiographic changes**

317 Chest radiographs at baseline and day two were available for 47 patients (26
318 urokinase, 21 placebo). In the urokinase group, size of effusion decreased, but in the
319 placebo group there was no significant change (urokinase: 35% hemithroax
320 opacification (SD 20) at enrolment, 23% (SD 15) at day two; placebo group: 42% (SD
321 21) at baseline and 44% (SD 24) at day two (adjusted analysis for baseline %
322 opacification, mean difference, placebo vs urokinase -19%, 95% CI -28 to -11%,
323 $p\leq 0.001$).

324

325 **Hospital Stay**

326 Patients receiving urokinase had a shorter length of hospital stay (measured as time
327 from randomization to discharge in patients who survived hospital admission) mean
328 length of stay =6.2 days (SD 2.7) versus 8.7 days (SD 6.5) in the placebo group
329 (adjusted hazard ratio 1.6 days (95% CI 1.0 to 2.6), $p=0.049$).

330

331 **Fluid Output**

332 Data were available for 24/36 patients in the urokinase group and 19/35 patients in
333 the placebo group. There was no significant difference in total pleural fluid drainage
334 between the groups from randomisation to tube withdrawal, with a mean drainage
335 volume of 358ml in the urokinase group (SD 644) and 257ml in the placebo group
336 (SD 402, adjusted mean difference 169ml (95% CI -111 to 448ml) (p=0.24).

337

338 **Change in blood parameters from baseline to day three**

339 There was no difference in change in haemoglobin, prothrombin time or activated
340 partial thromboplastin time (APTT) between the two groups from baseline to day
341 three (see eTable 1). Platelet counts were higher in those treated with urokinase
342 compared to placebo (adjusted difference 39 (95% CI 1.6 to 76, p=0.041).

343

344 **Quality of Life**

345 There was no difference in self-reported health status or overall quality of life
346 between the groups at any time point (adjusted difference in health status 1.6%,
347 (95% CI -8.6 to 12), p=0.76; adjusted difference in quality of life 7.4% (95% CI -3.2
348 to 18), p=0.18).

349

350 **Adverse events**

351 Six serious adverse events occurred. Two deaths occurred within days zero to three
352 due to progression of underlying malignancy (one urokinase, one placebo), two
353 pleural infections (one urokinase, one placebo), one chest tube wound dehiscence
354 (placebo) and one post-pleurodesis chest pain delaying discharge (urokinase). No
355 intrapleural haemorrhage occurred, and one patient (receiving placebo) experienced
356 systemic (pelvic) bleeding.

357

358

359 **Discussion**

360 This randomised placebo controlled trial is the first to compare urokinase with
361 placebo for treatment of septated MPE, and the first intrapleural fibrinolytic trial to
362 assess clinically meaningful outcomes (dyspnea and pleurodesis). Our results
363 demonstrate no improvement in dyspnea or pleurodesis success following
364 intrapleural urokinase despite chest radiographic evidence of significant reduction in
365 size of pleural effusion.

366 Study participants in our selected population had a high mortality, demonstrating that
367 the septated MPE population is likely to represent advanced malignancy. This poor
368 survival means that interventions requiring hospital admission, such as talc
369 pleurodesis, should be carefully considered in this population.

370 We observed a small but statistically significant decrease in mortality in the urokinase
371 group, although it should be noted that fibrinolytics are not recognised to have anti-
372 tumour effects, mortality was a secondary outcome and there was an excess of
373 patients with lung cancer in the placebo group. This study was conceived before the
374 development of the LENT score for prognostication in patients with MPEs so data
375 was not collected to enable us to compare baseline prognosis between the
376 groups(17). Neither of the previous randomised studies of intrapleural fibrinolytics in
377 MPE reported mortality outcomes(8, 9), however this potential effect should be
378 subject to further studies.

379 Urokinase was associated with a decrease in hospital stay compared to placebo,
380 despite having no effect on dyspnea or fluid output, and in the presence of improved
381 chest radiograph appearance in the urokinase group. The reasons for shortened
382 hospital stay using urokinase are not clear, and require further investigation.

383 Our results support the findings of Okur, et al and Saydam, et al in the key finding
384 that lung re-expansion is improved but no change in pleurodesis success following
385 administration of intrapleural fibrinolytics is observed in patients with septated
386 MPE(8, 9). This improvement could be due to an increase in fluid output of
387 approximately 100ml in the urokinase group, although this difference did not reach
388 statistical significance. Although different fibrinolytics were used in these studies,
389 there is no reason to hypothesize any difference in efficacy between fibrinolytics.
390 Intrapleural urokinase was not associated with any adverse reactions, suggesting it is
391 safe for use in patients with MPE.

392 In light of these results, is it appropriate to insert a chest tube and attempt
393 pleurodesis in patients with a septated MPE which is unlikely to drain? Given the high
394 mortality demonstrated in this study, we propose that outpatient treatments (such as
395 therapeutic aspiration or indwelling pleural catheter insertion) in conjunction with
396 other palliative treatments for dyspnea (such as low dose opiates) may be more
397 appropriate for this patient group, aiming at providing dyspnea relief without a
398 hospital admission. Alternatively, thoracoscopy may allow more effective drainage
399 prior to pleurodesis in those able to tolerate this procedure.

400 This study has several limitations. The study did not reach the original recruitment
401 target. However, this occurred in light of new data on the minimal important
402 difference in VAS used for measurement of dyspnea. On the basis of the data
403 published during recruitment for this study, TIME3 would be adequately powered to
404 exclude a clinically meaningful change in dyspnea following intrapleural urokinase.
405 Completion of screening logs was variable between centres despite guidelines, with
406 some sites including all patients with a chest tube for MPE whereas other sites only
407 included patients fulfilling the eligibility criteria.

408 The TIME3 study results suggest important potential future areas of research.
409 Indwelling pleural catheters (IPC) are increasingly used in the treatment of patients
410 with MPE on the basis of randomised trials demonstrating improvement in dyspnea
411 and reduced hospital stay(18). Recognised IPC complications include blockage and
412 development of septations, which are increasingly treated with intrapleural
413 fibrinolytics. A retrospective case series suggested improvement in pleural fluid
414 drainage and radiographic appearance using intrapleural fibrinolysis(19), but this

415 study demonstrates these are not reliable surrogates for the key clinical outcomes of
416 dyspnea relief and pleurodesis success. This suggests that prospective controlled
417 trials are now required to assess the potential clinical benefit and harms of such
418 treatment in IPC patients.

419 In summary, intrapleural urokinase does not improve dyspnea or pleurodesis
420 success compared with placebo in patients with non-draining MPE treated with a
421 chest tube and should not be routinely used as an adjunct to pleurodesis. This
422 subgroup of patients have a high mortality and significant residual dyspnea despite
423 chest tube insertion, and alternative palliative measures should be considered for the
424 relief of dyspnea. The potential benefits of this treatment in improving hospital stay,
425 chest radiograph appearances and mortality should be further investigated.

426 **Table 1:** Baseline characteristics of the 71 trial patients by group.

	Placebo	Urokinase
	(N=35)	(N=36)
Age (yrs) mean (sd)	71.5 (8.3)	69.5 (10.5)
Female (%)	17 (49)	13 (36)
WHO Performance Status	21 (60)	21 (58)
0-2 (%)		
Histological tissue type		
(%)		
Lung	12 (34)	10 (28)
Mesothelioma	5 (14)	4 (11)
Breast	6 (17)	6 (17)
Gastrointestinal	1 (3)	3 (8)
Adenocarcinoma of unknown	2 (6)	1 (3)
primary		
Ovarian	1 (3)	2 (6)
Other	8 (23)	10 (28)
Previously pleurodesed	5 (14)	5 (14)
(%)		
Size 12 French chest drain	33 (94)	30 (83)
(%)		
% opacification of	42 (21)	35 (20)

hemithorax by effusion		427
(SD)		
Baseline VAS score (mm)	38 (25)	38 (28)
(SD)		

428 **Figure legends**

429 **Figure 1:** CONSORT diagram to summarise recruitment.

430 **Figure 2:** Mean change from baseline in VAS dyspnea following intrapleural
431 urokinase or placebo. Circles represent mean VAS dyspnea over 28 days for
432 individual participants, black line represents overall mean of group. Positive change
433 represents less breathlessness.

434 **Figure 3:** Kaplan-Meier curve of time to pleurodesis failure

435 **Figure 4:** Time to death by group

436

437

438 **Acknowledgments**

439 Prof Najib Rahman had full access to all the data in the study and takes responsibility
440 of the integrity of the data and the accuracy of the data analysis.

441 The National Cancer Research Institute and Syner-Med Ltd had no role in design
442 and conduct of the study; collection, management, analysis, and interpretation of the
443 data; preparation, review or approval of the manuscript; or decision to submit the
444 manuscript for publication.

445

446

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